

RESEARCH ARTICLE

N-Acetyltransferase 2 (NAT2) Acetylator Status among Systemic Lupus Erythematosus Patients from A Tuberculosis Endemic Area in Bandung, Indonesia

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Abstract

BACKGROUND: Systemic lupus erythematosus (SLE) patients living in Indonesia are prone to tuberculosis (TB) infection, since this country ranks second globally for TB prevalence. Isoniazid, an anti-tuberculosis (TB) drug, is metabolized by enzyme N-acetyltransferase 2 (NAT2) that is encoded by *NAT2* gene. *NAT2* haplotype, referring as acetylator status, may predispose as genetic factor in SLE development or complicate SLE therapy. This study explored the *NAT2* haplotypes and acetylator status among SLE patients living in a TB endemic area.

METHODS: Genomic DNA of 260 registered SLE patients at The Rheumatology Clinic of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia were isolated. *NAT2* gene was amplified and sequenced, then *NAT2* haplotypes and the acetylator status among SLE patients with or without TB history were determined and presented.

RESULTS: Most of SLE patients registered were female (n=250; 96.2%). The median age of patients when SLE was diagnosed for the first time was 27 years old (8-69 years), with organ involvement predominantly in musculoskeletal (80.8%) and mucocutaneous (73.1%). TB history, mostly pulmonary TB, was present in 23.1% of SLE patients of whom TB was diagnosed before SLE (10.4%) or after SLE (10.7%) or both before and after SLE (2%). The acetylator status was mostly intermediate (61.5%) with the *NAT2**4/*6B was the most prevalent haplotype (25.8%).

CONCLUSION: There is a high number of intermediate and low acetylator status among SLE patients. Since these SLE patients live in TB endemic area, the *NAT2* acetylator status determination among SLE patients before starting TB therapy may have clinical benefit to decrease a possible drug induced liver injury, and this warrants further study.

KEYWORDS: *NAT2*, acetylator, systemic lupus erythematosus, tuberculosis

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Introduction

Systemic lupus erythematosus (SLE) is a complex chronic condition due to abnormality of immune system. The etiology of SLE is still unknown, as the SLE immune system has lost their self-tolerance resulting in an immune dysregulation.(1) Recently, genetic involvement in SLE is becoming central, triggered by environmental *i.e.*, UV exposure, smoking and other stochastic factors such as hormonal factor, some infections and many other factors contributing to the development of disease.(2) Genome wide association studies have shown evidence and propose some candidate regions towards susceptibility to SLE from variation in many genes, especially in the host immune system. Certain genes involved in the pathway of toll like receptors (TLR) and type 1 interferon, immune signal transduction, immune complex processing may play roles in the SLE susceptibility.(3) Interestingly, genes *i.e.*, signal transducer and activator of transcription 4 (STAT4), protein tyrosine phosphatase non-receptor type 22 (PTPN22), Tumor necrosis factor, alpha-induced protein 3 (TNFAIP3), and many other genes that are expressed in SLE, these genes are also expressed in other autoimmune diseases, such as rheumatoid arthritis.(3)

Furthermore, various drugs may also induce SLE known as drug induced SLE (DILE), among others isoniazid (INH), a tuberculosis (TB) antibiotic, that is metabolized by N-acetyltransferase2 (NAT2) enzyme. (4) This catalytic enzyme, encoded by *NAT2* gene, has a pivotal role in detoxifies and inactivates some drugs for example hydrazine drugs, as well as xenobiotics, and also metabolizes carcinogenic arylamines and other chemicals in the liver.(5) Interestingly, INH, as one of the primary TB drugs, has been used as a model drug in silico to determine acetylation phenotype.(6)

The acetylation phenotype or acetylation rate varies from person to person.(7) Individual acetylation rate or acetylase status is classified into rapid, intermediate or slow acetylators, based on the co-dominant expression of *NAT2* haplotypes.(8) *NAT2* gene, located at chromosome 8p22, exhibits several variants, comprising *NAT2* haplotype. The haplotype heterozygous NAT2*4/*6 and homozygous NAT2*5/*5 has been reported to be more frequent in SLE patients, compared to control group of which the NAT2*5/*6 is more prevalent.(9) Interestingly, the slow acetylase individual may be prone to develop SLE later in life.(10)

Since the *NAT2* haplotype varies among population, the aim of this study was to determine the distribution of *NAT2* acetylase status which was explored among SLE patients with or without TB history from Bandung, Indonesia, as this country is a TB endemic area.(11)

Methods

Design of The Study

The design of this study was a descriptive cross-sectional study, exploring the *NAT2* acetylase status among SLE patients living in a TB endemic area, therefore, history of TB in SLE patients was assessed.

Recruitment of SLE Patients

This study was part of a larger SLE patient registry at The Rheumatology Clinic of Dr. Hasan Sadikin General Hospital (Dr. Hasan Sadikin Lupus Registry, (HSLR)). Consecutive clinical data of SLE patients registered during January 2016 to May 2018 were collected, including TB history and treatment. SLE patients were further grouped into SLE patients with or without history of TB. No exclusion criteria in this study. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) index and organ damage were assessed.(12) The study protocol was approved by the Ethical Research Committee of Medical Faculty, Universitas Padjadjaran No. 36/UN6.KEP/EC/2018.

DNA Extraction and Amplification

During a routine visit in the outpatients clinic, blood samples were collected into ethylenediaminetetraacetic acid (EDTA)-coated tubes. DNA was extracted and stored at -20°C according to the manufacturer's instructions (Qiagen, Hilden, Germany). *NAT2* gene was amplified in a final volume of 50 µL, containing of 1U polymerase chain reaction (PCR) MyTaq™ HS Master Mix (Bioline, London, UK), 20µM for each primer forward and reverse as published earlier (13), and 200ng DNA template. PCR was performed by PCR Thermal Cycler Eppendorf 5331 Mastercycler (Marshall Scientific, Hampton, USA) with PCR condition as followed: 95°C initiation phase for 3 min, followed by 35 cycles of denaturation at 95°C for 15 s, annealing at 50°C for 15 s, and elongation at 72°C for 60 s, and ended by a cycle of final extension at 72°C for 5 min. The PCR product was further sequenced for one direction of forward sequencing. *NAT2* gene variants were then aligned and acetylase status was determined.

Molecular Analysis of *NAT2* Variants and Acetylator Status Determination

Sequence of *NAT2* gene was analyzed using ClustalX for multiple alignments with sequence reference from GenBank (Acc. No. KR231610). Variants of *NAT2* gene were assessed and the acetylator status of SLE patients was determined and classified into three groups, including slow, intermediate and fast acetylator based on *NAT2* acetylator nomenclature (http://nat.mbg.duth.gr/Human%20NAT2%20alleles_2013.htm). In brief, fast acetylation is coded by wild-type *NAT2**4 alleles or *NAT2**13, while impaired acetylation has various alleles i.e. intermediate (heterozygous) or slow (homozygous) acetylator status was determined according to nucleotide change in 341 T>C (*NAT2**5), 590 G>A (*NAT2**6), 857 G>A (*NAT2**7). When sequences were found not in nomenclature yet, they were designated as 'ND (cannot determined)'.

Results

During January 2016 to May 2018, 264 consecutive SLE patients, older than 16 years old were registered at The Rheumatology Outpatient Clinic of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. Only 260 DNA of these SLE patients were successfully sequenced for *NAT2* haplotype and acetylator status was then determined. At

the time of inclusion in the study, only 245 (94.2%) SLE patients were still followed up, 9 were lost and 6 died due to infection, particularly caused by community acquired pneumonia.

SLE patients registered were predominantly female (96.2%; n=250) of whom 6% (n=20) were female >50 years old. The median age when SLE was diagnosed was 27 years old (range 8-69 years), and no statistical different ($p=0.824$) between male and female patients as shown in Table 1. Interestingly, 4.2% (n=11) of these SLE patients were diagnosed at young age of <15 years old, and 3.1% (n=8) were at older age of >50 years old. Most of the female SLE patients were non-smokers (76.1%; n=198 of 250) in contrast to male SLE patients who were active or passive smokers (60%, n=6 of 10). Of note, passive smokers were present in 49 of 250 (19.6%) female SLE patients (Table 1). As for clinical involvement, the most affected organs were musculoskeletal (80.8%) and mucocutaneous (73.1%) as depicted in Table 2. Disease activity of lupus at the time of subjects recruited was measured with SLEDAI showed that most patients (71.6%) had no disease activity. Up to 98.9% patients received methylprednisolone, while the other given drugs is described in Table 2.

Patients were grouped into SLE patients with no TB history (n=200; 76.9%), SLE patients with TB history, consisting TB history before SLE diagnosis (n=27; 10.4%), after SLE diagnosis (n=28; 10.7%) and in both periods of

Table 1. Clinical characteristics of SLE patients registered at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, during January 2016 to May 2018.

Characteristics	Male (n=10)	Female (n=250)	p- value
Age; years			
Median (min-max)	34.5 (16-47)	32 (16-73)	0.873
Age Group; n (%)			
<50 years	10 (3.8)	230 (88.4)	n.d
≥50 years	-	20 (7.6)	
Age at SLE diagnosis; years			
Median (min-max)	30.5 (13-42)	27 (8-69)	0.824
Age Group at SLE diagnosis; n (%)			
<15 years	1 (0.4)	10 (3.8)	n.d
15-50 years	9 (3.5)	232 (89.2)	
>50 years	-	8 (3.1)	
Smoking; n (%)			
Non-smoker	4 (40)	198 (79.2)	n.d
Active smoker	3 (30)	3 (1.2)	
Passive smoker	3 (30)	49 (19.2)	

SLE: systemic lupus erythromatosus; n.d not determined.

Table 2. Organ involvement, disease activity, SLE therapy and TB history during SLE period. among patients from Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

Categories	n (%)
Organ Involvement	
Musculoskeletal	210 (80.8)
Mucocutaneous	190 (73.1)
Nephritis	118 (45.4)
Hematological	86 (33.1)
Neuropsychiatric	45 (17.3)
SLEDAI*	
No Activity	189 (71.6)
Mild	66 (25)
Moderate	8 (3)
Severe	1 (0.4)
SLE Therapy	
Methylprednisolone	261 (98.9)
Azathioprine	143 (54.2)
Chloroquine	147 (55.7)
Cyclophosphamide	48 (18.2)
Methotrexate	10 (3.8)
Cyclosporine	16 (6.1)
Mycophenolate mofetil	14 (5.3)
TB history	
No TB history	200 (76.9)
TB history	60 (23.1)
TB pre SLE	
Pulmonary TB	15 (5.8)
Extra Pulmonary	12 (4.6)
TB post SLE	
Pulmonary TB	17 (6.5)
Extra Pulmonary	11 (4.2)
TB pre & post SLE	5 (2)

*SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

before and after SLE diagnosis (n=5; 2.0%) as shown in Table 2 with detailed pulmonary or extra pulmonary TB. All patients with TB history were asked for their TB treatment, and INH was noted as one of the drugs among TB regiment of all these patients.

***NAT2* Haplotype and Acetylator Status Among SLE Patients**

The sequences of *NAT2* gene variants were analysed in this study. The most prevalent variant was G590A (55.4%), consisting of heterozygous GA (45%) and homozygous AA (10.4%) as this variant was dominant in *NAT2**6

haplotype, while others were C282T (30.4%), T341C (16.9%), C481T (10.8%), A803G (16.9%), G857A (21.5%) (shown in Supplement 1). Analysis of the haplotype wild type *NAT2**4 (21.5%), haplotype *NAT2**6B (25.8%) and *NAT2**6A (12.7%) were the most prevalent haplotype in SLE patients from Bandung, Indonesia as shown in Table 3. The acetylator status among SLE patients from Bandung were detected in trimodale mode as fast acetylator (59 cases; 22.7%) consisted of *NAT2**4 wild type and *NAT2**12A (homozygous or heterozygous), and as intermediate (160 cases; 61.5%) and slow acetylator (37 cases; 14.3%). We have found new variants in *NAT2* gene in our samples (n4; 1.5%) that did not belong to known haplotype.

***NAT2* Acetylator Status and TB History Among SLE Patients**

There were 32 patients who had TB history before SLE was diagnosed of whom 27 had TB only before SLE diagnosis and 5 others had TB in both periods *i.e.*, before and after SLE diagnosis as shown in Table 4. Most of the SLE patients recovered well from TB infection.

Discussion

The immunopathogenesis of SLE is complex and not fully understood yet.(14) Gene interaction to some drugs and/or enzymes that metabolize certain drugs may play an important role. This is the first SLE study in Indonesia, exploring *NAT2* haplotypes and acetylator status among SLE patients recruited from SLE registry in TB endemic area Bandung, Indonesia.

The distribution of *NAT2* variants and haplotypes have been extensively studied in different ethnic groups. The most prevalent variant in our study is G590A (55.4%), while study in Brazil is G857A.(15) The distribution of the most prevalent *NAT2* haplotypes in our study are the wild type *NAT2**4 (21.5%), haplotype *NAT2**6B (25.8%) and *NAT2**6A (12.7%) (Table 3); and the acetylator status among SLE patients from Bandung fast acetylator (22.7%), intermediate (61.5%) and slow (14.3%). Slow acetylator may have impacted the TB therapy with the development of drug induced liver injury (DILI) or hepatotoxicity, as confirmed by several studies across population.(16-18) Therefore, individual with slow acetylator status may have been exposed with TB drugs longer, especially INH, and prone to develop SLE.(19)

Study in Japan showed that environmental factor such as cigarette smoking has been associated with increased risk

Table 3. Haplotype distribution among *NAT2* acetylator status of SLE patients registered at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

	<i>NAT2</i> Acetylator Status				Total (n)	%
	Rapid	Intermediate (heterozygous)	Slow	Unknown††		
NAT2*4 (wild type)	56	-	-	-	56	21.5
NAT2*12A	3	-	-	-	3	1.2
NAT2*5						
NAT2*5A	-	1	-	-	1	0.4
NAT2*5B	-	11	3	-	14	5.4
NAT2*5C	-	2	-	-	2	0.8
NAT2*5D	-	4	1	-	5	1.9
NAT2*5E	-	2	-	-	2	0.8
NAT2*5KA†	-	1	-	-	1	0.4
NAT2*5Q†	-	1	-	-	1	0.4
NAT2*5S†	-	1	-	-	1	0.4
NAT2*5T†	-	2	-	-	2	0.8
NAT2*5TA†	-	2	-	-	2	0.8
NAT2*5U†	-	11	-	-	11	4.2
NAT2*6						
NAT2*6A	-	6	27	-	33	12.7
NAT2*6B	-	67	-	-	67	25.8
NAT2*6F†	-	4	-	-	4	1.5
NAT2*6J†	-	23	-	-	23	8.8
NAT2*7						
NAT2*7A	-	17	-	-	17	6.5
NAT2*7B	-	1	6	-	7	2.7
NAT2*7C†	-	2	-	-	2	0.8
ND†	-	2	-	4	6	2.3
Total (n)	59	160	37	4	260	
%	22.7	61.5	14.3	1.5		100

NAT2 haplotype according to http://nat.mbg.duth.gr/Human%20NAT2%20alleles_2013.htm. ND (cannot determined): haplotype not in nomenclature yet; †: haplotype with unknown acetylator status, however, intermediate and slow acetylator status is determined according to nucleotide change in 341 T>C (NAT2*5), 590 G>A (NAT2*6), 857 G>A (NAT2*7); ††: unknown acetylator status.

to SLE, especially in individual with *NAT2* slow acetylator genotype.(9) Tobacco, the ingredients of cigarette, is classified into aromatic amines that needs to be detoxified by N-acetyltransferase enzyme. Passive smoker are prevalent among female SLE patients (19.2%) where the household members especially male are smokers.

Furthermore, study results of *NAT2* acetylator status in relation with SLE are conflicting. Eventhough slow acetylators are more prevalent in SLE patients compared to their healthy controls, 9 others studies showed lack of evidence for this association.(20,21) In our study, we are lacking of control group, therefore, the real association of

slow acetylator status and susceptibility to SLE could not be further analyzed.

Although the result is contradicting, we have drawn special attention on TB history among SLE patients as Indonesia harbors TB patients being the second of TB prevalence globally, and thus the chance of getting Mycobacterium tuberculosis infection is high and latent TB infection may exist. Infection is known as one of the common trigger factors for SLE. Study showed that Mycobacterium tuberculosis infection may have a role in precipitating SLE through immunomodulatory action. (22,23) In the other hand, SLE patient is vulnerable to

Table 4. *NAT2* acetylator status distribution in association with TB prevalence and TB therapy outcome among SLE patients with history of TB registered at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

	Total	NAT2 Acetylator Status			
		Rapid N (%)	Intermediate N (%)	Slow N (%)	Unknown†† N (%)
TB prevalence					
SLE with no TB history	200	43 (21.5)	129 (64.5)	29 (14.5)	4 (2.0)
SLE with TB history					
before SLE diagnosis	27	8 (29.6)	15 (55.6)	4 (14.8)	-
after SLE diagnosis	28	6 (21.4)	18 (64.3)	4 (14.3)	-
before & after SLE diagnosis	5	2 (40.0)	3 (60.0)	-	-
TB therapy outcome					
before SLE diagnosis*	32				
Recovered	26	7 (21.9)	15 (46.9)	4 (12.5)	
Relapse	5	2 (15.6)	3 (9.4)	-	
Failed	1	1 (3.1)	-	-	
after SLE diagnosis**	33				
Recovered	26	6 (18.2)	16 (48.5)	4 (12.1)	
Relapse	5	2 (6.1)	3 (9.1)	-	
Failed	1	-	1 (3.0)	-	
Died	1	-	1 (3.0)	-	

SLE: Systematic Lupus erythematosus; TB: tuberculosis; n.d: not determined. * SLE patients with TB before SLE and with TB before & after SLE diagnosis together. ** SLE patients with TB after SLE and with TB before & after SLE diagnosis together. ††: unknown acetylator status, however, intermediate and slow acetylator status is determined according to nucleotide change in 341 T>C (*NAT2**5), 590 G>A (*NAT2**6), 857 G>A (*NAT2**7).

infection due to dysregulation of multiple aspects in the immune system.(24) Interestingly, some antibiotics against infections in particular may also predispose the SLE development, known as DILE.(19)

Mycobacterium tuberculosis infection may develop after SLE. This infection is possible due to various immunosuppressive or corticosteroid agent needed for SLE therapy, either infection from the neighboring people or latent TB infection re-activation. An extra pulmonary tuberculosis infection is common (25) although in our study extra pulmonary TB has an equal percentage compared to pulmonary TB. When TB infection after SLE is diagnosed, the *NAT2* acetylator status determination may have beneficial of clinical importance, not only for SLE chemotherapy but also for TB therapy. Further studies on pharmacokinetic, -dynamics and -genetic in SLE drugs may have a great interest.(26)

The Limitation of The Study

This *NAT2* acetylator status study does not compare SLE patients as cases vs. healthy individuals as controls, therefore, this study is limited and can not explore the

analysis regarding the role of *NAT2* acetylator status and SLE susceptibility. As for TB history, no laboratory data on liver function, thus, drug induced liver injury can not be assessed. An integrative SLE and TB collaborative care need to be implemented.

Conclusion

The distribution of intermediate and slow *NAT2* acetylator status among SLE patients from Bandung, Indonesia is predominant as high as 65.4% and 11.9%, respectively. In the area where TB prevalence is high, acetylator status determination among SLE patients may have an important role before INH therapy to guide for successful TB treatment.

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